Curcumin: A new candidate for melanoma therapy?

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Melanoma remains among the most lethal cancers and, in spite of great attempts that have been made to increase the life span of patients with metastatic disease, durable and complete remissions are rare. Plants and plant extracts have long been used to treat a variety of human conditions; however, in many cases, effective doses of herbal remedies are associated with serious adverse effects. Curcumin is a natural polyphenol that shows a variety of pharmacological activities including anti-cancer effects, and only minimal adverse effects have been reported for this phytochemical. The anti-cancer effects of curcumin are the result of its anti-angiogenic, pro-apoptotic and immunomodulatory properties. At the molecular and cellular level, curcumin can blunt epithelial-to-mesenchymal transition and affect many targets that are involved in melanoma initiation and progression (e.g., BCI2, MAPKS, p21 and some microRNAs). However, curcumin has a low oral bioavailability that may limit its maximal benefits. The emergence of tailored formulations of curcumin and new delivery systems such as nanoparticles, liposomes, micelles and phospholipid complexes has led to the enhancement of curcumin bioavailability. Although in vitro and in vivo studies have demonstrated that curcumin and its analogues can be used as novel therapeutic agents in melanoma, curcumin has not yet been tested against melanoma in clinical practice. In this review, we summarized reported anti-melanoma effects of curcumin as well as studies on new curcumin formulations and delivery systems that show increased bioavailability. Such tailored delivery systems could pave the way for enhancement of the anti-melanoma effects of curcumin.

Plant extracts and their active compounds have long been regarded as promising candidates to treat a variety of human diseases; however, natural products or their synthetic analogues may cause serious side-effects.1,2 Since natural products generally show less toxicity than synthetic compounds, they have been the subject of increasing research interest particularly for the treatment of cancer and its complications.3,4 Curcumin is a natural polyphenol extracted from the rhizomes of the plant Curcuma longa L. (turmeric).3,5 Mounting evidence indicates that curcumin plays significant roles in several biological processes and possesses several pharmacological properties which are beneficial to the treatment of human diseases. These pharmacological effects include antioxidant,7–10 anti-inflammatory,11–13 lipid-modifying,14–17 anti-arthritic,10,18 cardio-protective,19,20 anti-ischemic,21 anti-depressant,6,22 anti-diabetic,23 neuro-protective,24 cognition-enhancing25–28 and anti-atherosclerotic29,30 properties. These studies confirmed that curcumin can affect various targets such as cytokines, protein kinases, multiple transcription factors, adhesion molecules, inflammatory mediators and redox state enzymes.3,30

Melanoma arises from malfunctioning of normal melanocytes in the epidermis. In recent decades, the incidence of melanomas has increased at an alarming rate, particularly in Western populations where individuals tend to have lighter skin color and thus less sun protection.31–33 Patients with advanced malignancies have poor prognoses with average survival times of 3–11 months.31 Many melanomas with early diagnoses can be removed by surgical resection with no further problems to the patient. However, melanomas
notoriously have high metastatic potential, and once metas-
tasis occurs, they are very difficult to treat. Therefore, the
search for novel therapies against melanoma is warranted.
Many studies introduced curcumin as a novel molecule that
can be used for the treatment of melanoma. These reports
have employed curcumin and its analogues using various
delivery systems in melanoma therapy.

With respect to the pharmacokinetic profile of curcumin,
it has been observed that utilization of novel delivery systems
such as micelles and nano-particles could increase curcumin
bioavailability, thereby potentiating its anti-tumor effects in
melanoma. In addition, the expression of certain microRNAs,
known to influence many molecular and cellular processes,
can be altered by curcumin. This review summarizes the
findings of various studies on the utilization of curcumin in
melanoma therapy. Research on the tailored formulations
with novel drug delivery systems, and synthetic analogues of
curcumin are also discussed.

Curcumin as a Therapeutic Agent in Melanoma
For hundreds of years, turmeric has been utilized as a treat-
ment for conditions like inflammation, neoplasms, etc. In
recent years, molecular targets and various cellular and
molecular pathways that are affected by curcumin have been
evaluated and identified.

Several studies on animals and humans have indicated that
curcumin can be safe at various doses. These reports
showed that curcumin could be tolerated even at very high
doses. Although obtaining high doses of curcumin in humans
is a problem, with the help of novel drug delivery systems,
the problem of using bulky doses could be resolved. In
addition, various studies have indicated that even low
doses of curcumin have therapeutic effects against various
diseases.

Low solubility and lack of a high systemic bioavailability
is regarded as a major problem in utilization of curcumin as a
therapeutic agent. Several studies have reported low or
undetectable plasma/tissue levels of free curcumin. However,
it must be taken into account the metabolites and degra-
dation products of curcumin, like curcumin sulfate,
curcumin glucuronide and tetrahydrocurcumin possess signif-
icient and, in some cases, similar or stronger biological and
pharmacological activities compared with curcumin.

Another proof for the activity of curcumin metabolites is the
biological activity of curcumin treated with alkali, which is
known to destabilize curcumin.

Many studies have shown that in multi-factorial diseases
such as cancer, some agents that affect various cellular and
molecular targets may be of higher therapeutic value. Among
these agents, curcumin shows suitable properties and
can affect different pathways in various diseases such as can-
cer. Melanoma is known as one of the important malign-
ancies that shows poor diagnosis and high resistance to
different treatment regimens. Mounting evidence indicates
that curcumin affects several molecular and cellular pathways
involved in melanoma pathogenesis such as MST1, JNK,
Foxo3, Bim-1, Mcl-1, BCI-2, Bax and JAK-2/STAT-3
making it a promising therapeutic agent to be used against
this type of cancer. Figure 1 shows various cellular and
molecular pathways influenced by curcumin in melanoma.

In a research, Bush et al. investigated the molecular path-
ways targeted by curcumin during apoptosis in human mela-
noma cells. They revealed that curcumin can induce cell death
in various melanoma cell lines with wild-type or mutant p53.
They also showed that curcumin induces apoptosis dose- and
time-dependently in melanoma cell lines. Their results
indicated that curcumin induced cell death via different path-
ways e.g., activation of caspases-3 and caspases-8 but not
caspase-9 via a membrane-mediated mechanism. In addition,
it was shown that curcumin could induce Fas receptor aggre-
gation in a FasL-independent manner. Previous studies
showed that suppression of receptor aggregation inhibited
curcumin-induced cell death. Some evidence revealed that
melanoma cells with mutant p53 show strong resistance to
conventional chemo-therapeutic agents. Therefore, curcumin
might be able to overcome the chemo-resistance of these cells
and open new horizons in cancer therapy.

Zhang et al. investigated the effects of curcumin on the
migration, proliferation and invasiveness of human mela-
noma cells. In the referred study, A375 cells were cultured,
passaged and treated with different concentrations of curcu-
min. Different concentrations of curcumin induced signifi-
cant changes in the morphology of A375 cells. The results
indicated that curcumin can significantly inhibit the migra-
tion and invasion of A375 cells compared with the control
group. Curcumin (50, 25 and 12.5 mM) significantly
decreased the number of A375 cells in the treated group. In
addition, the rates of apoptosis at the concentrations of 6.25
and 12.5 mM of curcumin were significantly higher than
those of the control group. On the other hand, phosphoryla-
tion levels of STAT-3 and JAK-2 at the concentrations of 10
and 20 mM of curcumin were significantly lower than those
in the control group. Bcl-2 protein expression at the concen-
trations of 1, 2.5, 5, 10 and 20 mM of curcumin was signifi-
cantly lower compared with the control group. In this latter
study, curcumin showed various effects such as anti-
proliferative and pro-apoptotic activities on A375 cells, and
the inhibition of JAK-2/STAT-3 signaling pathway was sug-
gested as one of mechanisms through which curcumin exerts
its effects on this cell line.

Philip et al. showed that osteopontin (OPN) induces
nuclear factor kappa B (NF-kB) through pro-matrix metallo-
proteinase 2 activation via IkappaB alpha/IKK signaling path-
ways which are downregulated by curcumin in a melanoma
mouse model. Their results indicated that curcumin could
inhibit NF-kBB-DNA binding, NF-kB transcriptional activity
and the OPN-induced translocation of p65. The authors
revealed that curcumin could inhibit OPN-induced cell
migration, extracellular matrix invasion and cell proliferation.
Also, curcumin can synergistically induce apoptotic
morphological changes by OPN in melanoma cells. Moreover, curcumin suppresses OPN-induced tumor growth in nude mice, and inhibits the activation of OPN-induced tumor and the levels of pro-MMP-2 expression. Table 1 illustrates the effect of curcumin on melanoma reported by different studies.58

An important mediator of the cell stress response is heat shock protein 90 (Hsp90), which has been reported to be upregulated in melanoma,59 and its inhibition, along with the inhibition of Hsp70, has been reported to enhance the sensitivity of melanoma cells to the anti-tumor effects of hyperthermia.60 Interestingly, there is evidence showing that curcumin synergistically enhances the anti-tumor effect of bortezomib in melanoma through inhibition of Hsp90 expression.61 Hemeoxygenase/biliverdin reductase (HO/BVR) is another main component of the cell stress response.62,63 This system facilitates the degradation of heme which is toxic if produced in excess or unbalanced under redox conditions.64 Recently, it was found that HO/BVR system is upregulated in melanoma patients.65 Interestingly, among the pharmacological effects of curcumin, enhancement of the cell stress response was mediated through HO/BVR.66 Hence, regulation of cell stress response could be regarded as a potential mechanism curcumin may affect development and progression of melanoma.

Parallel to the identification of many anti-cancer effects of curcumin, some studies have indicated that this agent could cause potential adverse effects under specific conditions.67,68 There is some data showing that curcumin could induce chromosomal alterations and DNA damage, both in vitro and in vivo.69 However, Kurien and colleagues indicated that curcumin does not bind or intercalate into DNA.70 It should be noted that this binding could be caused by the solvent of curcumin (e.g., organic solvents) rather than the compound itself.70 Inhibition of several drug-metabolizing enzymes including CYP3A4, glutathione-S-transferase and UDP and UDP-glucuronyl transferase is another effect of curcumin which may induce potential drug interactions.71 Although such sporadic reports on the potential adverse effects of curcumin exist and necessitate further evaluations, the trend in

Figure 1. Cellular and molecular pathways affected by curcumin in melanoma. MAPK: mitogenactivated protein kinase; STAT: signal transducer and activator of transcription; NF-κB: nuclear factor kappa-light chain-enhancer of activated B cells; PARP: poly(ADP-ribose) polymerase. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Table 1. Effects of curcumin on melanoma as reported by various studies

<table>
<thead>
<tr>
<th>Dose</th>
<th>Target gene</th>
<th>Effects</th>
<th>Model (in vitro/in vivo/human)</th>
<th>Type of cell line</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–80 mM</td>
<td>mPTP</td>
<td>Facilitating mPTP death pathway</td>
<td>In vitro</td>
<td>WM-115, B16</td>
<td>72</td>
</tr>
<tr>
<td>10, 20 mM</td>
<td>JAK-2/STAT-3</td>
<td>Anti-proliferative and pro-apoptotic activities</td>
<td>In vitro</td>
<td>A375</td>
<td>57</td>
</tr>
<tr>
<td>10 μM</td>
<td>−</td>
<td>Inhibition of proliferation and stimulation of differentiation</td>
<td>In vitro</td>
<td>B16F10</td>
<td>73</td>
</tr>
<tr>
<td>15 μM</td>
<td>Mcl-1, Bcl-2, Bax, caspase-8, Caspase-3, NF-κB, p38, p53</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>A375, MV3, M14</td>
<td>74</td>
</tr>
<tr>
<td>30–40 μM</td>
<td>caspase-3/7</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>B16F10</td>
<td>75</td>
</tr>
<tr>
<td>10 μM</td>
<td>ERK/Akt</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>A375</td>
<td>76</td>
</tr>
<tr>
<td>30–100 μM</td>
<td>mPTP, ANT-1</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>WM-115</td>
<td>77</td>
</tr>
<tr>
<td>0.2–5 μg/ml</td>
<td>caspases 8, 9, 3</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>G-361, A375</td>
<td>78</td>
</tr>
<tr>
<td>25 μM/ml</td>
<td>MST1, INK, Foxo3, Bim-1</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>B16 and WM-115</td>
<td>79</td>
</tr>
<tr>
<td>2.5 mM</td>
<td>MRP1, GSTM1</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>CAL1</td>
<td>80</td>
</tr>
<tr>
<td>&lt; 5 μM</td>
<td>−</td>
<td>Decreasing cell growth</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>81</td>
</tr>
<tr>
<td>50 μM</td>
<td>−</td>
<td>Inhibition of tumorigenesis and angiogenesis</td>
<td>In vitro, in vivo</td>
<td>B16F10, B16F10, A375, SK-Mel-28</td>
<td>82</td>
</tr>
<tr>
<td>10⁻⁵ M</td>
<td>PDE1A</td>
<td>Anti-proliferative effect</td>
<td>In vitro</td>
<td>B16F10</td>
<td>83</td>
</tr>
<tr>
<td>20 μM</td>
<td>−</td>
<td>Inhibition of melanogenesis</td>
<td>In vitro</td>
<td>B16F10</td>
<td>84</td>
</tr>
<tr>
<td>50 μM</td>
<td>NFXB, MT1-MMP, MMP-2</td>
<td>Inhibition of tumor growth and decrease migration</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>85</td>
</tr>
<tr>
<td>1.25–10 μM</td>
<td>PI3K/Akt/GSK 3β, ERK, p38 MAPK</td>
<td>Inhibits melanogenesis</td>
<td>In vitro</td>
<td>B16</td>
<td>86</td>
</tr>
<tr>
<td>High dose</td>
<td>−</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>G361, A375</td>
<td>87</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>EphA2, PI3K, MMP-2, MMP9</td>
<td>Inhibition of tumor growth and vasculo-genic mimicry</td>
<td>In vitro</td>
<td>B16F10</td>
<td>88</td>
</tr>
<tr>
<td>10 μM</td>
<td>Caspase 3, Caspase 9, Bcl-XL, X-Iα</td>
<td>Induce apoptosis</td>
<td>In vitro</td>
<td>B16, WM-115</td>
<td>89</td>
</tr>
<tr>
<td>10 μM</td>
<td>MITF, MEK/ERK, PI3K/ Akt</td>
<td>Suppressive activity on α-MSH-stimulated melanogenesis</td>
<td>In vitro</td>
<td>B16F10</td>
<td>90</td>
</tr>
<tr>
<td>10–30 μM</td>
<td>caspase-9, caspase-3</td>
<td>Induce apoptosis</td>
<td>In vitro</td>
<td>M21, SP6.5</td>
<td>55</td>
</tr>
<tr>
<td>20 μM</td>
<td>PRL-3</td>
<td>Inhibition of metastasis</td>
<td>In vitro, in vivo</td>
<td>B16, B16BL6</td>
<td>91</td>
</tr>
<tr>
<td>20 μM</td>
<td>STAT1, STAT5, IFN-alpha, IFN-gamma, interleukin-2</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>A375, Hs294T</td>
<td>92</td>
</tr>
<tr>
<td>50 μM</td>
<td>Akt, NF-κB, Bcl-x, Erk, VEGF, cyclin D1</td>
<td>Blocks tumor formation</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>93</td>
</tr>
<tr>
<td>−</td>
<td>bcl-2, P53</td>
<td>Apoptosis induction</td>
<td>In vivo</td>
<td>B16</td>
<td>94</td>
</tr>
<tr>
<td>75 μM</td>
<td>eIf2α, GADD 153, aspases-3/7, Bcl-2</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>B16F10</td>
<td>95</td>
</tr>
<tr>
<td>50 μM</td>
<td>COX-2, cyclin D1, NF-κB</td>
<td>Apoptosis induction</td>
<td>In vivo</td>
<td>B16F10</td>
<td>96</td>
</tr>
</tbody>
</table>
findings is in favor of the acceptable safety of this compound. Moreover, conducted clinical trials of curcumin have shown the safety of curcumin for human use, even in studies administering highly bioavailable preparations of curcumin. It is also interesting to note that curcumin has been affirmed with a GRAS (generally recognized as safe) status by the US Food and Drug Administration.

Curcumin Analogs as Powerful Tools in Melanoma Therapy

Mounting evidence indicates that curcumin has multiple biological effects that make it a promising therapeutic candidate to be used in the treatment of several diseases such as cancer. On the other hand, it was observed that this agent has low oral bioavailability which led to the development of curcumin analogues (such as DM-1, EF24, D6 and CDF) with better anti-cancer effects and bioavailability.52 DM-1, one of the curcumin analogues, has shown anti-tumor effects in various in vitro and in vivo models.107,108 It has been confirmed that this compound is not only a suitable anti-cancer agent with anti-metastatic and anti-proliferative activities but also it has minimal side effects on normal cells.109, 110 Table 2 shows various curcumin analogues that can be used in melanoma therapy.

Commercial curcuminoids include curcumin, demethoxy-curcumin and bisdemethoxycurcumin. Most of the studies assessing the effects of curcumin against melanoma have been conducted with curcumin. Therefore, the impact of demethoxy and bisdemethoxy analogues, which are known to differ with curcumin in some properties,111 in reducing the progression of melanoma remains to be clarified. Four major strategies that could be used to improve the pharmacokinetic profile and enhance the delivery of curcumin are (i) Liposomes, micelles and phospholipid complexes; (ii) Glucuronidation/metabolism interference via co-administration of curcumin with adjuvants like piperine; (iii) Nanoparticles and (iv) Emulsifying or dispersing agents. Below, some of the studies on these forms of curcumin in melanoma are summarized.

In a study, Lo et al. reported that two compounds namely, 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (BHPHTO) and bisdemethoxycurcumin (BDMC) can inhibit the proliferation of melanoma cells. Moreover, Faião-Flores et al. revealed that curcumin analogue DM-1, alone or in combination with dacarbazine (DTIC), shows anti-tumor effects as it

<table>
<thead>
<tr>
<th>Dose</th>
<th>Target gene</th>
<th>Effects</th>
<th>Model (in vitro/in vivo/human)</th>
<th>Type of cell line</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 μM</td>
<td>c-myc, caspase-3</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>A375</td>
<td>97</td>
</tr>
<tr>
<td>6.1–7.7 μM</td>
<td>NF-κB, IKK</td>
<td>Antiproliferative and apoptotic</td>
<td>In vitro</td>
<td>C32, G-361, WM 266-276</td>
<td>54</td>
</tr>
<tr>
<td>30 μM</td>
<td>GSTP1, MRp1</td>
<td>Inhibition of the multidrug resistance</td>
<td>In vitro</td>
<td>A375</td>
<td>98</td>
</tr>
<tr>
<td>18, 27 μM</td>
<td>–</td>
<td>Inhibition of growth of B16-R melanoma</td>
<td>In vitro, in vivo</td>
<td>B16-R</td>
<td>99</td>
</tr>
<tr>
<td>15 μM</td>
<td>MMP-2</td>
<td>Anti-metastatic</td>
<td>In vitro</td>
<td>B16 F10</td>
<td>100</td>
</tr>
<tr>
<td>50 μM</td>
<td>iNOS, NF-κB</td>
<td>Apoptosis and cell cycle arrest</td>
<td>In vitro</td>
<td>A375</td>
<td>101</td>
</tr>
<tr>
<td>2.6, 1.9 μM</td>
<td>GST</td>
<td>Inhibition of the multidrug resistance</td>
<td>In vitro</td>
<td>CAL1</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>Nm23, E-cadherin</td>
<td>Anti-metastatic properties</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>103</td>
</tr>
<tr>
<td>50, 100 μM</td>
<td>OPN, NF-κB</td>
<td>Apoptosis induction</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>58</td>
</tr>
<tr>
<td>30 μM</td>
<td>Caspases-3/8</td>
<td>Apoptosis induction</td>
<td>In vitro</td>
<td>MMAN, MMRU, RPEP, PMWK, Sk-mel-2, Sk-mel-5, Sk-mel-28 c, MEWO</td>
<td>56</td>
</tr>
<tr>
<td>125 μg/ml</td>
<td>COX-I, COX-II</td>
<td>Antioxidant and anti-inflammatory activities</td>
<td>In vitro</td>
<td>SKMEL-28, M14, UACC-62</td>
<td>104</td>
</tr>
<tr>
<td>25 μM</td>
<td>GST</td>
<td>Inhibition of the multidrug resistance</td>
<td>In vivo</td>
<td>IGR-39</td>
<td>105</td>
</tr>
<tr>
<td>200 nmol/kg</td>
<td>–</td>
<td>Inhibition of lung metastasis</td>
<td>In vivo</td>
<td>B16F10</td>
<td>106</td>
</tr>
</tbody>
</table>
inhibited melanoma progression in a melanoma mouse model. In addition, no toxicological changes were observed in organs such as the spleen, kidneys, liver and lungs after the administration of DM-1, either alone or in combination with DTIC. DM-1 in combination with DTIC improved the recovery from anemia induced by melanoma and immunomodulation. It was found that DM-1 alone and in combination with DTIC induces apoptosis via the cleavage of caspase-8, 2,3 and 2,9. These results indicated that DM-1 shows therapeutic effects on melanoma via a preferential intrinsic apoptotic pathway by decreasing Bcl-2/Bax ratio.

In another study, Pisano et al. indicated that D6, a curcumin analogue, has anti-tumor activity against melanoma and neuroblastoma cells. This study revealed that α,β-unsaturated ketone D6 shows stronger therapeutic effects in inhibiting melanoma growth in comparison with curcumin. Various experiments were done in this study such as clonogenic assay, TUNEL assay, annexin-V staining and caspases activation assay, and PARP cleavage assay. These experiments confirmed that D6 is more effective in the treatment of melanoma and neuroblastoma when compared with curcumin. Hence, this data suggested that D6 can be considered as a good candidate for new therapies against neural crest-derived tumors.

Novel Therapeutic Approaches for Curcumin Targeting in Melanoma
Various studies on bio-distribution, absorption, elimination and metabolism of curcumin have indicated that this agent has rapid metabolism, poor absorption and rapid elimination from the body. Therefore, low systemic bioavailability of oral curcumin is known as a major limitation of its use. However, it should be considered that many of the metabolites and degradation products of curcumin, possess strong biological and pharmacological activities.

### Table 2. Various curcumin analogs in melanoma therapy

<table>
<thead>
<tr>
<th>Type of curcumin</th>
<th>Dose</th>
<th>Target gene</th>
<th>Model (in vitro/in vivo/human)</th>
<th>Type of cell line</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydrocurcumin</td>
<td>Dependent manner</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16F-10</td>
<td>116</td>
</tr>
<tr>
<td>Salicyl curcumin</td>
<td>Dependent manner</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16F-10</td>
<td>116</td>
</tr>
<tr>
<td>Curcumin III</td>
<td>Dependent manner</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16F-10</td>
<td>116</td>
</tr>
<tr>
<td>D6</td>
<td>17.5 mg/kg</td>
<td>Caspase-3 and 7</td>
<td>In vitro, in vivo</td>
<td>LB24, CN-MelA, GR-Mel, WM266-4, 1, 3443, M14</td>
<td>114</td>
</tr>
<tr>
<td>Curcumin ferrocenyl derivatives</td>
<td>17.9 μM</td>
<td>–</td>
<td>In vitro</td>
<td>B16</td>
<td>117</td>
</tr>
<tr>
<td>(2E,6E)−2,6-bis-(2,5-Dimethoxybenzylidene)cyclohexanone</td>
<td>50 μM</td>
<td>tyrosinase,</td>
<td>In vitro</td>
<td>B16</td>
<td>118</td>
</tr>
<tr>
<td>Curcumin-13c</td>
<td>20 μM</td>
<td>FGF-R1, EGFR, Btk, Mink, Ret, Itk</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>119</td>
</tr>
<tr>
<td>Curcumin compound C5</td>
<td>0.71 μg/ml</td>
<td>Tubulin polymerization inhibitory</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>120</td>
</tr>
<tr>
<td>DM-1</td>
<td>5 μM</td>
<td>TNF-R1, caspase 8</td>
<td>In vitro, in vivo</td>
<td>B16F10, A375</td>
<td>113</td>
</tr>
<tr>
<td>DM-1</td>
<td>75 μM</td>
<td>Mcl-1, Bcl-xL</td>
<td>In vitro</td>
<td>SK-MEL-5 and A375</td>
<td>121</td>
</tr>
<tr>
<td>FLLL32/62</td>
<td>2 μM or 4 μM</td>
<td>STAT3</td>
<td>In vitro</td>
<td>A375, HT144 Hs294T</td>
<td>122,123</td>
</tr>
<tr>
<td>D6</td>
<td>270 nM</td>
<td>p53, PI3K/Akt, NF-κB</td>
<td>In vitro, in vivo</td>
<td>LB24Dagi</td>
<td>124</td>
</tr>
<tr>
<td>Gercumin II</td>
<td>250 μM</td>
<td>–</td>
<td>In vitro</td>
<td>SK-MEL-28</td>
<td>125</td>
</tr>
<tr>
<td>Bilidemethoxycurcumin (BDMC)</td>
<td>25–100 μM</td>
<td>–</td>
<td>In vitro</td>
<td>A2058, B16-F10</td>
<td>112</td>
</tr>
<tr>
<td>Deketene curcumin</td>
<td>20 μM</td>
<td>G2 arrest</td>
<td>In vitro</td>
<td>B78H1</td>
<td>115</td>
</tr>
<tr>
<td>Curcumin-biphenyl derivatives</td>
<td>1, 10 μM</td>
<td>–</td>
<td>In vitro</td>
<td>WM266, CN, LB24Dagi, PNP</td>
<td>126</td>
</tr>
<tr>
<td>DM-1</td>
<td>83 μM</td>
<td>Caspase-3, –8 and –9</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>35</td>
</tr>
<tr>
<td>NC 2067</td>
<td>2.0–2.4 μM</td>
<td>–</td>
<td>In vitro</td>
<td>A375</td>
<td>127</td>
</tr>
</tbody>
</table>
Several studies utilized different approaches to overcome the aforementioned limitations. Using adjuvants can be a suitable approach to block curcumin metabolic pathways and improve its bioavailability. Delivery systems such as liposomes, nanoparticles, micelles and phospholipid complexes have been proposed to improve the pharmacokinetic properties of curcumin for cancer therapy. For example, micelles and phospholipid complexes can improve the gastrointestinal absorption of curcumin which results in higher plasma levels. Another strategy is to enhance the aqueous properties of curcumin for cancer therapy. For example, plexes have been proposed to improve the pharmacokinetic advantages as they are highly biocompatible and easy to make, and possess a suitable capacity of loading and releasing curcumin. Moreover, curcumin’s cellular uptake is improved with dipeptide NPs.

In another study, Loch-Neckel et al. examined the effect of orally administered chitosan-coated polycaprolactone NPs containing curcumin on metastatic melanoma in the lungs. Their results indicated that curcumin could decrease cell viability and induce apoptosis in B16F10 melanoma cells. They found that curcumin significantly reduces the expression of metalloproteinases in melanoma cells. Several studies showed that metalloproteinases are associated with the proliferation and migration of melanoma cells. The utilization of chitosan-coated NPs containing curcumin decreased pulmonary tumor formation in a melanoma lung metastasis model. In addition, histological analyses indicated a few small nodules of melanoma in lungs of mice treated with this system. Hence, curcumin-containing chitosan-coated polycaprolactone NPs may be a suitable system for the treatment of malignant melanoma.

**Curcumin and MicroRNAs in Melanoma**

MicroRNAs (miRNAs) are known as small and noncoding RNAs that can suppress gene expression at post-transcriptional levels via sequence-specific interactions with the 3’-untranslated regions (UTRs) of cognate mRNA targets. In addition, miRNAs are involved in the regulation of various key cellular processes such as apoptosis, proliferation, differentiation and development. Alterations in miRNA expression have been observed in a number of cancers, including melanoma. These alterations can arise from either genetic or epigenetic changes. It has been suggested that dietary components may modulate miRNA expression. Few studies have investigated the effect of curcumin on the expression of miRNAs in melanoma. Table 4 illustrates various miRNAs affected by curcumin in different cancers.

Dahmke et al. revealed that curcumin intake can affect miRNAs in murine melanoma. They indicated that miR-205-5p was the most significantly altered miRNA. This latter study showed that oral administration of curcumin can influence the miRNA signature of engrafting melanoma. Dahmke et al. evaluated the effects of curcumin in a melanoma model, which was established by the injection of murine B78H1 cells in the flank of C57BL/6 mice. Curcumin-containing diet (4%) was administered two weeks prior to the injection of tumor cells until the end of the experiment. The results indicated that curcumin feeding significantly decreases the growth of the flank tumors and substantially alters miRNA...
expression signature in tumors. For example, miR-205-5p was expressed over 100 times higher in the treatment groups compared with the control group. MiRNAs can have various targets in melanoma cells. Western blot analyses indicated that some targets such as proliferating cell nuclear antigen (PCNA) and anti-apoptotic B-cell CLL/lymphoma 2 (Bcl-2) were significantly downregulated in the treatment groups. This study proposed that there are alterations in the miRNA expression in engrafting curcumin-treated melanoma and miR-205-5p was the most significantly altered miRNA.

Diphenyldifluoroketone (EF24) is known as a curcumin analogue with anti-tumor effects that are mediated via inducing apoptosis and arresting cell cycle. Zhang et al. investigated the effect of EF24 on miR-33b in melanoma cells. They revealed that at noncytotoxic concentrations, EF24 is able to suppress epithelial-to-mesenchymal transition (EMT)

### Table 3. Novel curcumin delivery systems in melanoma therapy

<table>
<thead>
<tr>
<th>Type of curcumin</th>
<th>Dose</th>
<th>Target gene</th>
<th>Model (in vitro/in vivo/human)</th>
<th>Type of cell line</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin-based micelle</td>
<td>–</td>
<td>IL-6, CCL2, TNF-α, IFN-γ</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>30</td>
</tr>
<tr>
<td>Curcumin -FAP-ac - Cpg</td>
<td>–</td>
<td>Indolamine-2,3-dioxygenase</td>
<td>In vitro, in vivo</td>
<td>B16</td>
<td>53</td>
</tr>
<tr>
<td>Curcumin - RGD-PEG-PLA</td>
<td>–</td>
<td>–</td>
<td>In vitro</td>
<td>B16</td>
<td>52</td>
</tr>
<tr>
<td>Chitosan-coated liposomes-containing curcumin</td>
<td>2.5 μM</td>
<td>–</td>
<td>In vitro</td>
<td>B16F10</td>
<td>134</td>
</tr>
<tr>
<td>Curcumin – ANPs</td>
<td>30 μM</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B6F10</td>
<td>133</td>
</tr>
<tr>
<td>Methionine-dehydrophenylalanine-curcumin NPs</td>
<td>25 mg/kg</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16</td>
<td>136</td>
</tr>
<tr>
<td>Curcumin-RGD-lpNPs</td>
<td>20 mg/kg</td>
<td>–</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>137</td>
</tr>
<tr>
<td>Curcumin- MBCSPs</td>
<td>500 μg/ml</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>138</td>
</tr>
<tr>
<td>Curcumin- β- Cyclodextrin</td>
<td>14 μM</td>
<td>–</td>
<td>In vitro</td>
<td>A375</td>
<td>139</td>
</tr>
<tr>
<td>Curcumin- β- Cyclodextrin-gemini surfactant</td>
<td>14 μM</td>
<td>–</td>
<td>In vitro</td>
<td>A375</td>
<td>139</td>
</tr>
<tr>
<td>Chitosan-coated nanoparticles containing curcumin</td>
<td>100 mM</td>
<td>MMP-2, MMP-9</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>36</td>
</tr>
<tr>
<td>Curcumin/magnetite nanoparticles</td>
<td>66.0 μM</td>
<td>–</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>140</td>
</tr>
<tr>
<td>Curcumin – chitin nanogels</td>
<td>0.1–1.0 mg/ml</td>
<td>–</td>
<td>In vitro</td>
<td>A375</td>
<td>141</td>
</tr>
<tr>
<td>Curcumin – HP-β-CD</td>
<td>300 μg/ml</td>
<td>G2/M stage</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>142</td>
</tr>
<tr>
<td>Curcumin – PEO-PCL</td>
<td>10, 80 μM</td>
<td>–</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>143</td>
</tr>
<tr>
<td>Curcumin – Muc18</td>
<td>167–335 nM</td>
<td>NF-κB</td>
<td>In vitro, in vivo</td>
<td>B16F10</td>
<td>144</td>
</tr>
<tr>
<td>Curcumin plus PDMP</td>
<td>10 μM</td>
<td>PI3K/AKT</td>
<td>In vitro</td>
<td>WM-115 and B16</td>
<td>145</td>
</tr>
<tr>
<td>Curcumin–nanocapsules</td>
<td>6 mg/kg</td>
<td>–</td>
<td>In vitro</td>
<td>B16-F10</td>
<td>146</td>
</tr>
<tr>
<td>EF-24-FFRmk-fVIIa</td>
<td>1.5 μM</td>
<td>–</td>
<td>In vitro</td>
<td>RPMI-7951</td>
<td>147</td>
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<tr>
<td>Curcumin – XGO-b-PCL</td>
<td>1–100 μM</td>
<td>–</td>
<td>In vitro</td>
<td>B16F10</td>
<td>148</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MiRNA</th>
<th>Type of curcumin</th>
<th>Cancer</th>
<th>Expression in cancer</th>
<th>Target gene</th>
<th>Model</th>
<th>Type of cell line</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-33b</td>
<td>EF24</td>
<td>Melanoma</td>
<td>Upregulation</td>
<td>E-cadheri, STAT3</td>
<td>In vitro</td>
<td>Lu1205 and A375</td>
<td>156</td>
</tr>
<tr>
<td>miR-205-5p</td>
<td>Curcumin</td>
<td>Melanoma</td>
<td>Upregulation</td>
<td>Bcl-2, PCNA</td>
<td>In vitro,</td>
<td>B78H1</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In vivo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-21</td>
<td>EF24</td>
<td>Melanoma</td>
<td>Downregulation</td>
<td>NF-kB, JAK-STAT, PTEN, PDCD4</td>
<td>In vitro,</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In vivo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-34a</td>
<td>Curcumin</td>
<td>Colorectal</td>
<td>Upregulation</td>
<td>–</td>
<td>In vitro</td>
<td></td>
<td>157</td>
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<tr>
<td>miR-27a</td>
<td>Curcumin</td>
<td>Colorectal</td>
<td>Upregulation</td>
<td>-</td>
<td>In vitro</td>
<td></td>
<td>157</td>
</tr>
<tr>
<td>miR-7/let-7a,b,c,d, miR-26a, miR-101, miR-146a, miR-200b,c</td>
<td>Curcumin/diflourinated-curcumin</td>
<td>Pancreatic</td>
<td>Upregulation</td>
<td>EZH2, Notch-1, CD44, EpCAM</td>
<td>In vitro</td>
<td>AsPC-1, BxPC-3/AsPC-1 and MiaPaCa-2</td>
<td>158,159</td>
</tr>
<tr>
<td>miR-192-5p/215</td>
<td>Curcumin</td>
<td>Lung</td>
<td>Upregulation</td>
<td>PS3</td>
<td>In vitro, In vitro</td>
<td>H460, A427</td>
<td>160</td>
</tr>
<tr>
<td>miRNA-186*</td>
<td>Curcumin</td>
<td>Lung</td>
<td>Downregulation</td>
<td>caspase-10</td>
<td>In vitro</td>
<td></td>
<td>161</td>
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<tr>
<td>miR-125a-5p</td>
<td>Curcumin</td>
<td>Nasopharyngeal carcinoma</td>
<td>Downregulation</td>
<td>TP53</td>
<td>In vitro</td>
<td>HONE1</td>
<td>162</td>
</tr>
<tr>
<td>miR-9</td>
<td>Curcumin</td>
<td>Ovarian</td>
<td>Upregulation</td>
<td>Akt/FOXO1</td>
<td>In vitro</td>
<td>SKOV3</td>
<td>163</td>
</tr>
<tr>
<td>miR-205</td>
<td>PLGA-CUR NPs</td>
<td>Prostate</td>
<td>Upregulation</td>
<td>STAT3, AKT, Mcl-1, Bcl-xL</td>
<td>In vivo</td>
<td>LNCaP</td>
<td>164</td>
</tr>
<tr>
<td>miR-19</td>
<td>Curcumin</td>
<td>Breast cancer</td>
<td>Upregulation</td>
<td>PTEN, p-AKT, p-MDM2, p53</td>
<td>In vitro</td>
<td>MCF-7</td>
<td>165</td>
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<tr>
<td>miR-200a/b</td>
<td>Curcumin</td>
<td>Hepatocellular carcinoma</td>
<td>Upregulation</td>
<td>Bcl-2, Bad</td>
<td>In vitro</td>
<td>HepG2, HepG5</td>
<td>166</td>
</tr>
<tr>
<td>miR-15a/16-1</td>
<td>Curcumin</td>
<td>Leukemia</td>
<td>Upregulation</td>
<td>WT1</td>
<td>In vitro</td>
<td>K562, HL-60</td>
<td>167</td>
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<tr>
<td>miR-203</td>
<td>Curcumin</td>
<td>Bladder</td>
<td>Upregulation</td>
<td>Akt2, Src</td>
<td>In vitro</td>
<td>T24, J82 and TCCSUP</td>
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</tbody>
</table>

PLGA-CUR NPs: poly(lactic-co-glycolic acid)-curcumin nanoparticles.
and cell motility of melanoma cell lines such as A375 and Lu1205. In addition, EF24 suppressed HMG2 expression at mRNA and protein levels. MiR-33b can directly bind to 3’ untranslated region (3’-UTR) of HMG2 and suppress its expression. It was shown that miR-33b inhibition or HMG2 over-expression reverses EF24-mediated suppression of EMT. Moreover, EF24 modulates the focal adhesion assembly, Src, FAK and RhoA activation, and HMG2-dependent actin stress fiber formation via targeting miR-33b. Hence, these results propose that EF24 can suppress melanoma metastasis by upregulating miR-33b and concomitantly decreasing HMG2 expression.156

Yang et al confirmed that EF24 targets NF-κB and miRNA-21, and possesses a promising anti-tumor activity.39 EF24 has been reported to inhibit the NF-κB pathway in DU145 human prostate cancer cells and B16 murine melanoma cells. Moreover, EF24 induced apoptosis in these cells apparently via inhibiting miR-21 expression, and also improved the expression of several miR-21 target genes, e.g., PDCD4 and PTEN. This molecule inhibited miR-21 expression and lung metastasis, prolonged animal survival and increased the expression of miR-21 target genes in a mouse model of melanoma. Moreover, EF24 enhanced the expression of potential tumor suppressor miRNAs and inhibited the expression of oncogenic miRNAs, such as miR-21. These findings proposed that EF24 shows anti-cancer activities via regulating NF-κB pathway and miRNA expression.39

Conclusion
Melanoma, a malignant tumor of melanocytes, is one of the most aggressive types of malignancies. Although melanoma comprises <5% of all skin cancers, it is responsible for the majority of skin cancer-related deaths. At early stages, melanoma can be treated by surgical resection; however, most often it progresses to the invasive stage and does not respond to conventional treatments largely due to the development of multi-drug resistance. Hence, new therapies are required to overcome the limitations of conventional therapies. Several lines of evidence have indicated that curcumin affects key pathways that are involved in different cancers such as melanoma. It seems that this molecule plays an important role in cancer therapy. Several targets at the cellular and molecular levels (e.g., signaling pathways, transcription factors and miRNAs) are affected by curcumin in melanoma. Hence, curcumin can be regarded as a promising agent in the treatment of melanoma. Nevertheless, utilization of curcumin is associated with some limitations such as rapid metabolism, low oral absorption and rapid elimination from the body. These limitations may attenuate efficacy and decrease the therapeutic effects of curcumin. New formulations and novel delivery systems have opened a new window into the landscape of treatment of various diseases such as melanoma with curcumin. Finally, most of the evidence on the efficacy of curcumin against melanoma and other types of cancer pertains to preclinical studies. Although some clinical evidence exists that favors the benefits of curcumin supplementation in cancer patients,168-170 clinical evidence is still scarce and a thorough outcome study is yet to be performed. Hence, clinical proof-of-concept investigations are required to verify the translational value of the reported anti-tumor effects of curcumin in animal and cellular models of cancer. However, further evidence from prospective clinical trials is required to decipher the place of curcumin in the clinical management of melanoma.

References


33. Dec 8;−.

49. Kurien BT, Dillou SP, Dorry Y, et al. Curcumin does not bind or intercalate into DNA and a...
Mini Review


93. Faiaro-Flores F, Suarez JA, Soto-Cerrato V, et al. Bcl-2 family proteins and cytoskeleton changes...


